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Serial Evaluation of Haemostasis Following Acute Trauma Using Rotational Thromboelastometry in Cats

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Abstract

The objective of this prospective clinical study was to describe the coagulation abnormalities and incidence of acute traumatic coagulopathy (ATC) in traumatised cats over the first 24 h after admission.

In the 26 included cats with acute (<5h) trauma, blood samples for rotational thromboelastometry (ROTEM) were taken at presentation and 6/24 h thereafter. ROTEM tracings were defined as hypo- or hypercoagulable if ≥ 2 of the following parameters were above or below institutional reference intervals: clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), maximum lysis (ML), or maximum clot elasticity (MCE). ATC was defined as hypocoaguability at presentation. Injury severity scores, treatment and survival to discharge were retrieved from patient records.
The incidence of ATC was 15% and the most common ROTEM abnormalities in cats with ATC was CT and CFT prolongation in both extrinsic and intrinsic ROTEM profiles. After 24 h, compared to presentation, significantly more cats were hypercoagulable (P=0.047) and none of the cats showed hypocoagulopathy. Cats with ATC received significantly more blood transfusions (P=0.008).

The incidence of ATC in cats is higher than previously reported. Clotting time and CFT prolongations seem to be more common than hyperfibrinolysis and 53% of the cats became hypercoagulable within 24 h. While the clinical relevance of ATC in cats needs to be investigated, cats presenting with ATC required significantly more blood transfusions.

Vetsuisse Fakultät, Universität Zürich (2019)

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Departement für Kleintiere, Klinik für Kleintierchirurgie

Serielle Evaluation der Hämostase mittels Rotationeller Thromboelastometrie nach akutem Trauma bei Katzen

Zusammenfassung

Das Ziel dieser prospektiven, klinischen Studie war das Beschreiben der Hämostase und das Auftreten von akuter traumatischer Koagulopathie (ATC) in schwerverletzen Katzen in den ersten 24 h nach Trauma.

Von 26 Katzen mit akutem (<5 h) Trauma wurden Blutproben für die Rotationelle Thromboelastometrie (ROTEM) initial und 6/24 h danach genommen. ROTEM Messungen wurden als hypo- oder hyperkoaguabel bezeichnet, wenn ≥ 2 der folgenden Parameter über oder unter dem institutionellen Referenzintervall lagen: clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), maximum lysis (ML) oder clot elasticity (MCE). ATC wurde als Hypokoagulabilität bei Eintritt definiert. Schweregrad der Verletzungen, Behandlung und Überleben bis zur Entlassung wurden miteinbezogen.
Das Auftreten von ATC war bei 15% und die am häufigsten veränderten ROTEM Parameter in Katzen mit ATC waren CT und CFT Verlängerungen in den intrinsischen und extrinsischen ROTEM Profilen. Nach 24 h waren signifikant mehr Katzen hyperkoaguabel (P=0.047) und keine zeigte mehr Hypokoagulopathie, verglichen mit den Eintrittswerten. Katzen mit ATC erhielten signifikant mehr Bluttransfusionen (P=0.008)

Das Auftreten von ATC in Katzen ist höher als bisher angenommen. CT und CFT Verlängerungen scheinen häufiger als Hyperfibrinolyse und 53% der Katzen wurden hyperkoaguabel nach 24h. Die klinische Relevanz von ATC bei Katzen muss noch untersucht werden, Katzen mit ATC benötigen jedoch signifikant mehr Bluttransfusionen.

Serial Evaluation of Haemostasis Following Acute Trauma Using Rotational Thromboelastometry in Cats

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Abstract

Objective The aim of this study was to describe coagulation abnormalities and incidence of acute traumatic coagulopathy (ATC) in traumatized cats over the first 24 hours after admission.

Study Design This was a prospective observational study at the university teaching hospital including 26 cats with acute (<5 hours) trauma. Blood was sampled for rotational thromboelastometry (ROTEM) parameters at presentation and 6 hours/24 hours thereafter. Rotational thromboelastometry tracings were defined as hypo- or hypercoagulable if ≥ 2 of the following parameters were above or below institutional reference intervals: clotting time, clot formation time (CFT), maximum clot firmness, maximum lysis or maximum clot elasticity. Hypocoagulability at presentation was defined as ATC. Injury severity scores, treatment and survival to hospital discharge were retrieved from patient records.

Results The incidence of ATC was 15% and the most common ROTEM abnormalities in cats with ATC were clotting time and CFT prolongation in both extrinsic and intrinsic ROTEM profiles. After 24 hours, compared with presentation, significantly more cats were hypercoagulable ($p = 0.047$) and none of the cats showed hypocoagulopathy. Cats with ATC received significantly more blood transfusions ($p = 0.008$).

Conclusion The incidence of ATC in cats is higher than previously reported. Clotting time and CFT prolongations seem to be more common than hyperfibrinolysis and 53% of the cats became hypercoagulable within 24 hours. While the clinical relevance of ATC in cats needs to be investigated, cats diagnosed with ATC required significantly more blood transfusions.

Keywords
- ATC
- ACoT
- coagulation
- fibrinolysis
- acute traumatic coagulopathy

Introduction

Acute traumatic coagulopathy (ATC) is a frequent finding in people with as many as 25 to 34% of severely injured trauma patients being diagnosed with a coagulopathy in the form of systemic hypocoagulation or hyperfibrinolysis upon hospital admission.[1] The pathomechanisms associated with ATC are complex and likely to be multifactorial and different theories are currently being investigated. Overall, ATC is believed to be a systemic reaction following severe injury and hypoperfusion associated with trauma and shock.[2,3] One discussed pathomechanism is based on the protein C anticoagulant pathway, which seems to play a major role in the triggering of ATC in people.[4] Activated protein C directly inhibits FVIII and FV and binds and inactivates tissue plasminogen activator inhibitor-1, which explains the systemic hypocoagulopathy and hyperfibrinolysis, respectively.[2] In people, ATC develops

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immediately (minutes to hours) after trauma and is associated with a fourfold increase in mortality as well as increased blood loss and transfusion requirements.[5]

To date, only a few prospective clinical studies investigating ATC in dogs and cats have been published in veterinary medicine.[6–10] The study examining a population of 19 cats that were presented within 8 hours of trauma identified ATC in a single cat, whereas another cat was hypercoagulable.[8] In people, ATC has been described early after trauma[11] and the coagulation status is expected to change over time from hypo- to hypercoagulation.[12,13] This has recently been described in dogs with trauma.[10] The aim of this study was to describe coagulation abnormalities in traumatized cats by means of rotational thromboelastometry (ROTEM) at different defined time points after acute trauma and to determine the incidence of ATC in traumatized cats. We hypothesized that the presence of ATC would be higher early after trauma.

Materials and Methods

Cats that were presented within 5 hours after trauma between July 2016 and December 2017 were eligible to enter the study. Cats with a body weight lower than 2.5 kg, a known pre-existing disease or therapy interfering with haemostasis or receiving any other medication than an opioid, sedation or a bolus of maximum 10 mL/kg of a crystalloid fluid prior to the first blood sampling were excluded from the study. The study was approved by the Swiss federal ethics committee on animal research of the Canton of Zurich (ZH023/15). Informed client consent was obtained from all except stray cats.

Signalment, clinical signs, time after trauma and type of trauma were evaluated at the time of presentation. Transfusion requirement, hospitalization time and survival to hospital discharge were later recorded for each cat. If the traumatic event was not witnessed, the timeframe from the cat being last seen unharmed was taken as the time between trauma and admission.

To estimate injury severity, the animal trauma triage (ATT) score was calculated at admission as previously described.[14] Additionally, the acute patient physiology and laboratory evaluation $(APPLE)_{fast}$ score was determined.[15]

Blood samples for ROTEM and blood gas analysis (including lactate) as well as estimation of platelet numbers were obtained at presentation (0 hour), 6 hours and 24 hours after presentation. At each time point, approximately 1.5 mL of whole blood was sampled. The first blood drawing was taken from the newly inserted intravenous catheter (22-G) directly into a 1.3 mL 3.2% sodium citrate container (Micro tube 1.3 mL 9NC; Sarstedt AG, Nümbrecht, Germany) followed by collection of 0.2 to 0.5 mL of blood in a heparinized syringe (BD A-line blood gas syringe; Becton, Dickinson and Company, Plymouth, United Kingdom) for venous blood gas analysis (Rapidpoint500; Siemens Health care, Zürich, Switzerland). If blood flow from the catheter site was insufficient due to hypovolemia, a bolus of maximal 10 mL/kg of Ringer's acetate (Laboratorium Dr. Bichsel AG; Unterseen, Switzerland) IV was administered and the sampling was repeated approximately 10 minutes afterwards by direct venipuncture with a 21-G to 23-G cannula at the cephalic, saphenous or jugular vein. The additionally obtained blood samples at 6 and 24 hours after admission were taken through direct venipuncture at any of the above sites, using a 21-G cannula.

After sampling, citrated whole blood was placed into the 37°C pre-warming chamber of the ROTEM (ROTEM-Delta; TEM Innovations GmbH, Munich, Germany) device to rest for ~10 minutes before analysis.

Viscoelastic tests such as ROTEM measure the viscoelastic properties of whole blood and display the changes in viscoelasticity in a graph.[16] Different parameters are automatically determined. Several coagulation activators are available. The extrinsic temogram (EXTEM) test investigates clot formation by activation of the coagulation cascade through proprietary tissue factor (extrinsic pathway), while the intrinsic temogram (INTEM) test is activated by a contact activator (intrinsic pathway). The fibrin-clot can be determined by an EXTEM based assay with the addition of cytochalasin D to inactivate platelets fibrinogen temogram (FibTEM).

Rotational thromboelastometry analysis was performed by trained staff according to the manufacturer's instructions and an institutional standardized protocol based on international guidelines using single-use reagents.[17,18] Briefly, 300 µL of 37.0°C warm, citrated whole blood were incubated for 5 seconds with a single portion each of EXTEM, INTEM and FIBTEM reagent (TEM Innovations GmbH, Munich, Germany), followed by transferring the incubated blood sample into the ROTEM cuvette (Cup and Pin Pro, TEM Innovations GmbH, Munich, Germany) and attaching the cuvette to the pin. An automated pipette was used, and samples were analysed for 60 minutes. After measurement, all ROTEM tracings were visually evaluated for artefacts. Several parameters were recorded, including clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), clot firmness at 5 minutes (A5), maximum clot elasticity and maximum lysis (ML). The clotting time (CT) of each test describes the time until fibrin formation starts. The CFT displays the kinetics of clot formation and depends mainly on fibrinogen concentration and thrombocyte numbers. The MCF describes the maximal strength of the fibrin/thrombocyte clot in mm, while A5 describes clot firmness at 5 minutes after start of clot formation. Fibrinolysis was assessed with the ML in %, determined within 60 minutes of measurement. Maximal clot elasticity serves as a general parameter to describe clot strength. A green line identified in the FIBTEM tracing was defined as a MCF_{FIBTEM} of 0 mm and a CT_{FIBTEM} as 3600 second. Results were compared with institutional reference intervals.[19]

Blood smears were subsequently made from citrated whole blood and stained with a modified Wright-Giemsa stain (Diff Quick, Medion Diagnostics, Düdingen, Switzerland). Platelet number was manually examined in a high-power field magnification to estimate the platelet count and checking for clumping. If moderate-to-severe platelet clumping was identified, platelet count was considered normal. If available, the automated platelet count was additionally recorded.

Determination of Coagulation Status

Cats with two or more of the following ROTEM parameters below or above the reference interval at the investigated time point were defined as hypo- or hypercoagulable respectively: CT_{EXTEM}, CFT_{EXTEM}, MCF_{EXTEM}, ML_{EXTEM}, CT_{INTEM}, CFT_{INTEM}, MCF_{INTEM}, ML_{INTEM} and MCF_{FIBTEM}. Hyperfibrinolysis was defined as ML_{EXTEM} or $ML_{INTEM} > 10\%$. Cats showing hypocoagulopathy at presentation were defined as having ATC.

Statistical Methods

Data were extracted from the study protocol, ROTEM database and patient records and were entered into an electronic spreadsheet. Descriptive statistical analysis was performed using commercially available software (IBM SPSS Statistics for Windows, Version 23.0., IBM Corp, Armonk, New York, United States). Continuous data were tested for normality by Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation, while not normally distributed data are listed as median. Nonparametric data were assessed for associations using chi-squared or Fisher's exact test. Due to the small number of cats that showed ATC ($n = 4$), group comparisons were made using the nonparametric Mann–Whitney U test. Differences between ROTEM parameters at presentation and 6 hours/24 hours were analysed using Wilcoxon signed-rank test. Significance was set at $p < 0.05$.

Results

A total of 31 cats were enrolled between July 2016 and December 2017. Five cats were subsequently excluded because of missing data regarding time after trauma ($n = 3$), concurrent hepatic mass or hepatopathy ($n = 1$) and lack of trauma ($n = 1$).

The remaining 26 cats were represented by 25 European Short Hair and one Birman cat. Seventeen cats were castrated males, six spayed females, two males and one female. Median age was 5 years (range, 0.3–14 years) and mean weight 4.7 ± 1.2 kg (range, 2.6–7.0 kg). The traumatic event was not witnessed in 15 cases but was highly suspected based on history and clinical examination. Of the remaining 11 cats, 4 presented with high-rise syndrome, 3 were hit by car, 3 were bitten by a dog and 1 was impaled on a wooden stick. Mean time from traumatic event/last seen by owner to admission was 161 ± 69 minutes (range, 60–300 minutes). Seven cats received an opioid, four were treated with 3 to 10 mL/kg IV Ringer's acetate, one received midazolam (Dormicum; Roche Pharma (Schweiz) AG, Reinach, Switzerland) and one cat received medetomidine (Medetor; CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany) and ketamine (Ketanarkon 100; Streuli Pharma AG, Uznach, Switzerland) prior to blood sampling. A single cat of the ATC group received 3 mL/kg 7.2% NaCl (Laboratorium Dr. Bichsel AG) immediately prior to blood sampling.

Mean injury severity, based on the ATT score, was 6.0 ± 3 (range, 1–11). Seventeen cats suffered from polytrauma (more than one body region injured resulting in a life-threatening condition). Five of 26 cats were euthanized due to poor prognosis, including two cats shortly after presentation and three cats after the 24-hour measurement. The median total hospital stay was 6 days (range, 1–17 days). Three cats (two with ATC and one without ATC) received a fresh whole blood transfusion during hospital stay upon showing clinical and laboratory signs of severe anaemia.

Rotational thromboelastometry parameters and coagulation status at presentation are summarized in ►**Tables 1** and **2**. Sixteen cats presented normocoagulable, six hypercoagulable and four cats were hypocoagulable and were defined as presenting with ATC (►**Table 2**). Of the four cats with ATC, the abnormal ROTEM parameters were prolonged CT_{EXTEM} ($n = 4$), decreased MCF_{EXTEM} ($n = 1$), decreased $A5_{EXTEM}$ ($n = 1$), increased ML_{EXTEM} ($n = 1$), prolonged CT_{INTEM} ($n = 4$), prolonged CFT_{INTEM} ($n = 1$), decreased $A5_{INTEM}$ ($n = 1$), decreased MCF_{INTEM} ($n = 1$) and decreased MCF_{FIBTEM} ($n = 1$). A single cat showed hyperfibrinolysis and another one had an immeasurable MCF_{FIBTEM} in addition to being classified as presenting with ATC. The six hypercoagulable cats presented with the following ROTEM abnormalities: decreased CT_{EXTEM} ($n = 1$), decreased CFT_{EXTEM} ($n = 3$), increased MCF_{EXTEM} ($n = 2$), increased $A5_{EXTEM}$ ($n = 5$), increased MCF_{INTEM} ($n = 3$), increased $A5_{INTEM}$ ($n = 2$) and increased MCF_{FIBTEM} ($n = 3$). Two of these six cats with two or more signs of hypercoagulation showed a prolonged CT_{INTEM} ($n = 2$). Platelet count was available in 25 of 26 cats. Nine of 25 cats showed severe platelet clumping. Of the 16 remaining cats, the median estimated platelet number was 275,000/uL (range, 122,000–576,000/uL).

Coagulation Status at 6 Hours and 24 Hours

Rotational thromboelastometry parameters and coagulation status at 6 and 24 hours are summarized in ►**Tables 1** and **2**. Seven of 24 surviving cats were evaluated 6 hours after the first blood sampling. Two of these seven cats stayed normocoagulable, two stayed hypercoagulable, two cats that were hypocoagulable became normocoagulable and one cat that was initially normocoagulable became hypocoagulable within 6 hours. Four of the cats tested at 6 hours were additionally tested at 24 hours, resulting in a total of 13/24 surviving cats being re-evaluated 24 hours after presentation. Of the four cats presenting with ATC, two became hypercoagulable, one became normocoagulable and one was euthanized prior to any further testing. At presentation, more cats (4/26) showed hypocoagulopathy (ATC) compared with 24 hours (0/13), while identification of hypocoagulopathy at 6 hours was not different compared with presentation (1/7, $p = 0.366$). Significantly more cats showed hypercoagulability at 24 hours (7/13) compared with presentation (6/26) ($p = 0.047$). None of the cats showed hyperfibrinolysis at 6 hours or 24 hours.

Comparison of Cats with and without ATC

Differences between cats with and without ATC at presentation are summarized in ►**Tables 3** and **4**: CT_{EXTEM} and CFT_{EXTEM} and all INTEM parameters except ML_{INTEM} were significantly more hypocoagulable in cats with ATC compared with cats without ATC. Transfusion requirement was significantly higher in cats with ATC (2/4 vs. 1/22; $p = 0.008$). No other investigated clinical signs or laboratory parameters

Table 1 ROTEM parameters of 26 cats at presentation, 6 h and 24 h after acute trauma

		At presentation ($n = 26$)		6 h ($n = 7$)		24 h ($n = 13$)		
	Reference interval	Mean ± SD median	Range	Mean ± SD median	Range	Mean ± SD median	Range	*p*-Value[a]
EXTEM								
CT [s]	35–53	42	32–187	37 ± 4	33–43	33 ± 4	28–42	0.001
A5 [mm]	27–56	50 ± 11	20–70	47 ± 16	26–67	51 ± 12	27–67	0.092
CFT [s]	44–213	62	35–309	63	40–200	75	34–202	0.969
MCF [mm]	41–75	70	36–80	61 ± 8	55–79	69 ± 9	50–80	0.091
MCE		224 ± 71	57–393	238 ± 85	122–383	263	99–403	0.069
ML [%]	0–8	1	0–32	2	0–4	1	0–6	0.128
INTEM								
CT [s]	128–248	268	147–807	275 ± 105	166–431	357 ± 148	166–651	0.972
A5 [mm]	24–58	47 ± 9	20–68	53 ± 19	17–70	51 ± 10	30–64	0.028
CFT [s]	50–223	81	49–301	71	54–363	80	59–171	0.889
MCF [mm]	42–74	67	54–80	70 ± 11	50–81	72	50–82	0.002
MCE		204	67–401	152 ± 109	100–424	259	101–457	0.002
ML [%]	0–10	0	0–2	1	0–1	0	0–3	0.334
FIBTEM								
CT (s)		43	34–3600	34 ± 3	30–39	34 ± 6	28–47	0.001
MCF [mm]	3–10	7 ± 3	0–15	7 ± 4	0–15	12 ± 7	4–25	0.002
MCE		7 ± 4	0–18	8 ± 5	0–17	15 ± 9	4–33	0.003

Abbreviations: A5, amplitude at 5 minutes; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; MCE, maximum clot elasticity; ML, maximum lysis; ROTEM, rotational thromboelastometry; SD, standard deviation.
[a]Between presentation and 24 hours.

Table 2 Changes in coagulation status and platelet count over time in cats with acute trauma

Time point	At presentation	6 h	24 h
Parameter	n/N	n/N	n/N
Hypocoagulable/ATC	4/26	1/7	0/13
Normocoagulable	16/26	4/7	6/13
Hypercoagulable	6/26	2/7	7/13
Hyperfibrinolysis ($ML_{EXTEM} > 10\%$)	1/26	0/7	0/13
Thrombocytopenia (<150 10 × 3/uL)	8/22	NA	2/8
Hypofibrinogenemia (MCF_{FIBTEM} <2 mm)	1/26	1/7	0/13

Abbreviations: ATC, acute traumatic coagulopathy; NA, not assessed.

differed significantly (►**Table 3**). Presence of ATC was not associated with ATT score ($p = 0.096$), $APPLE_{fast}$ score ($p = 0.082$) or survival to hospital discharge ($p = 0.600$).

Discussion

Our study evaluating coagulation status in traumatized cats shows that both hypo- and hypercoagulopathy can be identified in cats presenting early after trauma and is the first to demonstrate changes in the coagulation status of traumatized cats over time. The incidence of ATC in our study population is higher than previously reported[8] (15 vs. 5%) and comparable to studies in dogs that also report a wide range (1–23%) of patients presenting with ATC.[6–8,10]

The encountered differences in incidences are multifactorial and include differences in ATC definition, sampling time after trauma and disease severity. The definition of ATC varies and there is no uniform definition of ATC in neither human nor veterinary medicine existing. Early studies defined ATC based on prolongations of plasmatic coagulation tests.[2,20,21] Recent studies in people prefer definitions based on viscoelastic tests[22–24] to evaluate global haemostasis rather than the coagulation cascade alone. We therefore chose to define ATC based on different ROTEM parameters.[22,25] For detecting coagulation abnormalities involving the initial coagulation cascade, CT_{EXTEM} and CT_{INTEM} were included. Both parameters correlate to plasmatic coagulation times.[19] Additionally, CFT was included to represent clot formation and MCF for the assessment of clot stability. The previous study identifying ATC in a single cat defined ATC as > 2 hypocoagulable parameters of a combination of plasmatic coagulation tests and thromboelastography parameters.[8] In people, ROTEM analysis is comparable to TEG; however, it is thought to be more sensitive for overall coagulation assessment of ATC.[26] While no feline studies compared TEG and ROTEM, a higher sensitivity of

Table 3 Clinical signs and laboratory parameters at presentation of 4 cats with ATC and 22 cats without ATC

	ATC ($n = 4$)			Non-ATC ($n = 22$)			
Parameter	**N**	**Median n/N**	**Range**	**N**	**Median n/N**	**Range**	***p*-Value**
Age [y]	4	6.25	1–12	22	4.4	0.3–14	0.864
Weight [kg]	4	4.5	4–6	22	4.7	2.6–7.0	0.918
Time after trauma [min]	4	188	120–240	22	150	60–300	0.389
ATT score [0–18]	4	8	5–11	22	5	1–9	0.096
APPLE score [0–50]	3	39	31–45	13	26	18–43	0.082
Heart rate [bpm]	4	155	90–210	22	200	150–260	0.096
Respiratory rate[bpm]	4	36	28–60	22	50	24–160	0.197
Temperature [°C]	4	36.4	32.0–37.7	22	37.3	32.0–38.9	0.935
Haematocrit [%]	4	37	22–39	22	38	29–46	0.389
Thrombocyte count [10 × 3/uL]	3	260	246–260	14	349	122–576	0.226
Thrombocytopenia [< 150,000/uL]	3	2/3		19	6/19		0.291
Intensive care stay [d]	4	7	1–8	22	2	1–13	0.150
Hospital stay [d]	4	9	1–17	22	5	1–16	0.295
Survival to hospital discharge [%]	4	3/4		22	18/22		0.600
Transfusion requirement	4	2/4		22	1/22		0.008

Abbreviations: ATC, acute traumatic coagulopathy; ATT score, animal trauma triage score; APPLE score, acute patient physiological and laboratory evaluation.

Table 4 ROTEM parameters at presentation of cats with and without ATC

		ATC ($n = 4$)		Non-ATC ($n = 22$)		
	Reference interval	**Median**	**Range**	**Median**	**Range**	***p*-Value**
EXTEM						
CT [s]	35–53	92	56–187	41	32–46	0.000
A5 [mm]	27–56	33	20–56	53	36–70	0.058
CFT [s]	44–213	169	79–309	58	35–93	0.001
MCF [mm]	41–75	58	36–71	71	49–80	0.130
MCE	NA	159	57–248	240	97–393	0.150
ML [%]	0–8	2	0–32	1	0–7	0.706
INTEM						
CT [s]	128–248	420	323–807	242	147–478	0.005
A5 [mm]	24–58	35	20–45	48	37–68	0.005
CFT [s]	50–223	158	123–301	71	49–126	< 0.001
MCF [mm]	42–74	58	40–67	68	60–80	0.016
MCE	NA	138	67–203	212	151–401	0.013
ML [%]	0–10	0	0–1	0	0–2	0.607
FIBTEM						
CT (s)	NA	122	40–3600	41	34–388	0.047
MCF [mm]	3–10	4	0–8	6	3–15	0.068

Abbreviations: A5, amplitude at 5 minutes; ATC, acute traumatic coagulopathy; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; MCE, maximum clot elasticity; ML, maximum lysis; NA, not available; ROTEM, rotational thromboelastometry.

ROTEM for identification of trauma-related changes could potentially account for the higher incidence of ATC in our study. Another reason for the higher incidence of ATC in our study population may be associated with trauma severity. In people and one canine study, the incidence of ATC increased with trauma severity.[7,20,27] Cats of our study presented with a median ATT score of 6 compared with 3 in the study by Gottlieb and colleagues. Based on the ATT score, our cats were more severely traumatized than the cats of the previous study. While there was a trend that cats presenting with ATC had a higher ATT score, larger studies are needed to evaluate this association.

Time-dependence may further be important to consider when evaluating ATC after trauma. As the median time from trauma to presentation was 90 minutes in the prior study compared with 161 minutes in our study, we do not expect time to account for the different incidence. Nevertheless, time after trauma has to be taken into account when evaluating coagulation status in cats with trauma as we were able to demonstrate the dynamic process of coagulation abnormalities with hypocoagulopathy being significantly less prevalent over time and no cat showing hypocoagulopathy 24 hours after presentation despite fluid administration and potentially further blood loss.

We also demonstrated that the percentage of hypercoagulable cats increases significantly over time. Human trauma patients are at risk to develop hypercoagulability and associated thromboembolism after surviving the initial traumatic coagulopathy, indicating some change in coagulation status over time.[12,28,29] The dynamic process leading to hypercoagulability could be explained by the discussed ATC pathomechanisms. Initially, the activated protein C pathway seems to be an important pathomechanism leading to both hypocoagulopathy and hyperfibrinolysis[4,30] and may escalate into an uncontrolled hypocoagulopathy within minutes to hours after trauma. Endogenous (coagulation, inflammation) and exogenous (trauma, medication) factors can alter coagulation status toward hypercoagulability or disseminated intravascular coagulation within hours to days.[28,31,32] Based on the degree of activation of haemostasis, confounding factors and the time point of analysis, trauma patients can, therefore, present normo-, hyper- or hypocoagulable. Our study identified cats presenting with hypercoagulability early after trauma showing that cats can both present hypo- or hypercoagulable. There are not enough data to support an effect of transfusion therapy on development of hypercoagulability, as only one cat received a transfusion (whole blood) within 24 hours and this cat changed from hypo- to normocoagulability.

Cats with ATC showed significant changes in several ROTEM parameters indicating both derangements in clot formation and clot stability. All INTEM parameters (ML excluded) were significantly different between the ATC and non-ATC group. Importantly, cats with ATC uniformly showed prolongations in clotting times (CT_{EXTEM}, CT_{INTEM}) and clot formation times (CFT_{EXTEM}, CFT_{INTEM}), while EXTEM and FIBTEM clot firmness was not significantly lower in cats with ATC. The single cat reported in the study by Gottlieb and colleagues[8] was defined as having ATC based on prolongations in prothrombin and partial thromboplastin time, supporting our finding that prolongations in clotting times seem to be more prominent than impairment of clot production and stability or hyperfibrinolysis. Interestingly, CT_{INTEM} remained prolonged in 10 of 13 cases even after 24 hours, whereas CT_{EXTEM} after 24 hours was in the hypercoagulable range in almost two-thirds of the cases presented with ATC. The clinical significance of CT_{INTEM} prolongation after 24 hours is unknown. One possible explanation of this finding could be autoheparinization. Autoheparinization is thought to occur after damage to the endothelium and shedding of the glycocalyx after trauma and hypotension and subsequent release of heparan sulphate, a prominent glycosaminoglycan of the glycocalyx, which has a heparan-like action and further contributes to the development of ATC.[33,34] There are no data supporting this theory in feline trauma cases, but the obvious prolongation of CT_{INTEM} despite an overall trend to hypercoagulability after 24 hours requires further investigations in this field.

While hyperfibrinolysis is an important consequence of ATC in people,[3,29,35,36] hyperfibrinolysis was found in only one cat in our study. This may be because hyperfibrinolysis is not a major problem in feline ATC, ROTEM analysis is not sensitive enough, or cats were not severely enough traumatized. We suspect the latter, as trauma severity and degree of protein C activation trigger different pathways of coagulopathy.[13]

Our study did not aim to describe associations between clinical signs, hypoperfusion, trauma severity and mortality with ATC as the number of cats with ATC is too low to allow for sufficient statistical power to detect a significant difference. Further studies are needed to evaluate these associations and to gain insight into the pathophysiology of feline ATC. Nevertheless, transfusion requirements were significantly higher in cats with ATC. Increased transfusion requirement is an important finding in people and should be investigated in a larger population of cats.[5,37,38]

Several limitations of the study need to be discussed. Not all cats could be re-evaluated at 24 hours and due to logistic reasons, only a few cats were evaluated at 6 hours. Despite the small number of cats re-evaluated, a significant change in haemostasis was identified. As this was a prospective clinical study including solely emergency patients, blood sampling site and technique were standardized as much as possible but were not performed by the same investigator and under the same conditions in all cases. Sampling technique and site of sampling may influence ROTEM results[17] and therefore our study results; however, the study conditions represent the clinical situation of a busy emergency clinic. An additional limitation is that some cats received fluids prior to ROTEM analysis and one of the four cats diagnosed with ATC was pre-treated with a bolus of 3 mL/kg hypertonic saline immediately prior to blood collection. *In vitro* administration of high dosages of hypertonic saline in people and dogs may be associated with coagulopathy due to platelet dysfunction, diminished clot propagation and clot strength, as well as impaired fibrin formation.[39,40] However, recent clinical studies in dogs do not report a hypocoagulable effect on ROTEM parameters after

a single bolus of 7.2% hypertonic saline.[41] Fluid administration may further lead to dilutional coagulopathy.[42,43] When excluding all cats with fluid treatment prior to blood sampling, the incidence of ATC would be only slightly lower with 14% and would not change the occurrence of hypercoagulability after 24 hours. As an additional limitation, trauma was not witnessed in all cats; based on traumatic injuries, trauma was suspected but the type of trauma could not be determined.

Conclusion

Acute traumatic coagulopathy does occur in cats with acute trauma, with a higher incidence than previously described. Clotting times and clot formation times seem to be most commonly prolonged and INTEM parameters seem to be superior in identifying ATC in cats. Coagulation status changes over time from a hypo- to hypercoagulable state, and while hyperfibrinolysis, thrombocytopenia and hypofibrinogenemia have been identified, they do not seem to play a major role in moderately traumatized cats.

Note

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Author Contribution

All authors contributed to conception of study, study design, acquisition of data, data analysis and interpretation and manuscript preparation. All authors drafted, revised and approved the submitted manuscript.

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Conflict of Interest

None declared.

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